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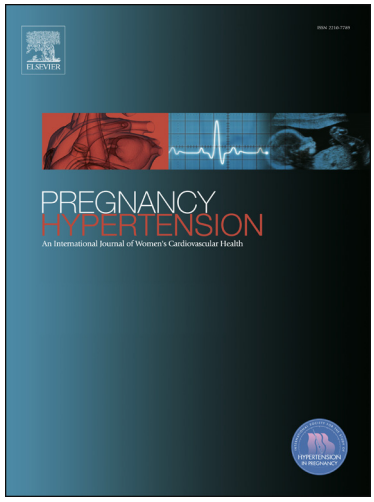

Early diagnosis of preeclampsia using placental growth factor: an operational pilot study in Maputo, Mozambique

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Early diagnosis of preeclampsia using placental growth factor: an operational pilot study in Maputo, Mozambique

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Abstract

In well-resourced settings, reduced circulating maternal free placental growth factor (PlGF) aids in either predicting or confirming the diagnosis of preeclampsia, fetal growth restriction, stillbirth, preterm birth, and delivery within 14 days of testing when pre-eclampsia is suspected. This operational pilot implementation of maternal plasma PlGF in women with suspected preeclampsia was conducted in six antenatal clinics in Maputo, Mozambique (six control clinics for comparison). The primary outcome was transfer to higher levels of care, following the informative PlGF assay. Of antenatal visits, 133/31,993 (0·42%) and 20/33,841 (0·06%) resulted in pre-eclampsia-related transfers of care for women attending intervention and control clinics, respectively ($p < 0·0001$). The clinic-to-delivery for women with low PlGF (<100 pg/ml) interval was shorter, (vs normal PlGF (median 10 days [IQR 1 - 25] vs 36 [11 - 83], $p < 0·0001$)). Low PlGF was associated with younger maternal age, higher blood pressure, earlier delivery, more therapeutic interventions, preterm birth, lower birth weight, and perinatal loss. In addition, one-third of hypertensive women with PlGF < 50 pg/ml suffered a stillbirth. In urban Mozambican women with symptoms and/or signs suggestive of preeclampsia, low maternal plasma PlGF concentrations are associated with increased risks of adverse pregnancy outcomes, especially early delivery and stillbirth. Therefore, introducing PlGF into the clinical care of women with suspected preeclampsia was associated with increased transfers to higher levels of care; low PlGF (<100 pg/ml) was associated with increased maternal and perinatal risks. PlGF <50 pg/ml is particularly associated with stillbirth in women with suspected preeclampsia.

Keywords

Preeclampsia; stillbirth; placental growth factor; diagnostic performance; operations research; global health

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Introduction

Pregnancy hypertension, especially preeclampsia, remains a significant contributor to adverse maternal and perinatal events in sub-Saharan Africa (1;2). Some women whose pregnancies are complicated by preeclampsia have evidence of angiogenic factor imbalance, with a surfeit of antiangiogenic factors (e.g., soluble fms-like tyrosine kinase-1 (sFlt-1)) and reduced proangiogenic factors (e.g., placental growth factor (PlGF)) (3-7).

Previously, we have confirmed the diagnostic performance of masked plasma PlGF in identifying women at increased risk of imminent delivery in clinics in Maputo, Mozambique (8); through the identification of pregnancy complications beyond preeclampsia, such as fetal growth restriction of placental origin (9). Therefore, we have proposed that PlGF should improve the provision of precision medicine to individual women and improve pregnancy outcomes for those with preeclampsia or related placenta-mediated complications in all settings. Thereby, clinicians in all settings may be better able to triage women with suspected complications to optimize the care of those most at risk within stretched health systems.

After completion of this technical evaluation study, we designed and conducted a pilot implementation study in health centers to assess the impact of PlGF in aiding the diagnosis and time-of-disease risk stratification of preeclampsia, and, thereby, improving appropriate interventions for, and timely care of women with preeclampsia. In contrast to clinical research methods, which typically focus on the health effects of an evidence-based practice, implementation studies typically focus on rates and quality of use of evidence-based practices rather than their effects (10).

Methods

Study design and context

This operational pilot study was conducted with screening and testing of women from 26 April to 30 November 2016. In this context, the objective of this operational pilot was to assess the probable impact of large-scale implementation of an intervention, PlGF testing, within a health system.

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All sites were in Maputo city, with six intervention sites (CS Bagamoyo, CS Chamanculo, CS Jose Macamo, CS Magoanine, CS 1 de Junho, CS 1 de Maio) and six control sites (CS Albazine, CS Catembe, CS Polana Canico, CS Pescadores, CS Xipamanine, CS Zimpeto). All sites offered prenatal care services, booked approximately 200 newly-identified pregnant women each month (i.e, 1400 new pregnancies per site), and had both on-site laboratory support and a maternity unit. CS Jose Macamo is associated with a general hospital. One site (CS 1 de Maio) has an ultrasound available, and CS Jose Macamo has access to the adjacent hospital's maternity unit ultrasound. The other four sites refer to the general hospital for ultrasounds, and any women referred need to use either public transport, car, or walk to get their ultrasound. Routine obstetric ultrasound was not offered at any sites, but limited to those deemed to be at high risk. Pregnancy dating was based upon last menstrual period and symphysis-fundal height. Intervention sites were matched, without randoimization, to control sites based on antenatal clinic volume, maternity ward, type of support, electricity and laboratory. Referral centers were shared between intervention and control sites.

Intervention sites

All pregnant women, irrespective of age, attending the respective prenatal clinics of the six intervention sites were screened for hypertension by the attending nurse, and if any given pregnant woman $<37^{+0}$ weeks' pregnant presented with any evidence preeclampsia (i.e., high BP, proteinuria, signs or symptoms) she would be a candidate for the PlGF test.

BP was measured with women sitting and with the right arm supported at the level of the heart as part of routine prenatal care, using Microlife BP A2 Basic, (Microlife AG, Widnau, Switzerland) fully automated BP monitors. BP measurement was repeated if hypertension (defined as either a systolic BP ≥ 140 mm Hg or a diastolic BP ≥ 90 mm Hg) was detected on the first reading and the lower reading recorded in the data collection form. Normotensive readings were not repeated. The presence of significant proteinuria (≥2+ by dipstick) was not an eligibility criterion.

At the time of the prenatal visit that triggered eligibility (suspected preeclampsia), venous blood was collected by the clinic nurse, plasma prepared, and PlGF assayed using the Alere

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Triage® monoclonal antibody-based immunoassay and meter (Alere, San Diego, CA), according to the manufacturer's instructions by the on-site laboratory technician. Maternal plasma PlGF concentrations were quantified within the measurable range of the assay (12 – 3000 pg/ml) and classified as either normal (≥100 pg/ml) or low (<100 pg/ml), as determined in our initial study (5). Clinical and research staff were not blinded to the PlGF results.

Pregnant women with suspected preeclampsia remained on site until the PlGF result was available and the nurse could use the result to complement diagnosis and determine whether or not to initiate a referral. If women were assessed to be too unwell to either await PlGF results, or even to have the blood draw, they were referred immediately. On occasion, the blood draw was completed, but the transport arrived prior to knowledge of the PlGF result and the woman was referred to a tertiary facility without delay.

Facility management, including delivery decisions, was made by clinicians who were not involved in the study and in compliance with Ministry of Health guidelines. The study protocol was approved by the National Bioethics Committee in Mozambique.

Patient information was collected from registries, patient charts and transfer logbooks at the prenatal care health facilities and maternity units. Dedicated study assistants were present at the intervention sites daily. They were stationed outside the antenatal clinic space and had access to all women screened for PlGF, to collect data at the time of screening. In addition, they were present when pregnant women returned for later antenatal visits or to the local maternity unit for delivery. Retrospective data were collected following delivery for women who delivered at referral maternity units. Two study assistants collected data two-to-three times a week to follow up transferred women, to ascertain whether or not they had been admitted or delivered, and the outcomes of mother and child. They attended the consulting rooms weekly, but did not interact with the women; rather, they relied solely on the available paper records (a more challenging task at referral facilities). In addition, they went weekly to search for data at referral facilities (these sites being the same referral sites for all the health centers). To support data collected from registries and patient charts, and fill in potential gaps due to deliveries occurring

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in the community, pregnant women enrolled in the intervention sites were contacted via either telephone or SMS, up to two times within the month after their due date of delivery.

Control sites

In the control sites, patient information was collected from registries and transfer logbooks at the prenatal care health facilities and maternity units. Two study assistants collected data two-to-three times a week, and patient chart data, including pregnancy outcomes, were not reviewed.

Outcomes

The primary outcome for analysis was transfer to higher levels of care, following the informative PlGF assay ('clinic'). Other outcomes of interest included: median time-to-delivery, confirmed diagnosis of preeclampsia, mode of delivery, intrauterine fetal death, and preterm birth ($<37^{+0}$ weeks). For outcome adjudication, preeclampsia was defined as hypertension and either significant proteinuria or other maternal organ dysfunction, according to the 2014 ISSHP criteria (11). Adjudication of a diagnosis of preeclampsia was performed by obstetricians not involved in the women's care but taking into consideration the PlGF results.

Sample size

The sample size was determined considering that the pilot was a two-arm multi-site observational cohort, with six health facilities in each of the intervention and control arms. Assuming that PIGF would be able to diagnose about 25% more cases in the intervention sites than conventional care in the control sites (above a baseline prevalence of 35% in women with suspected preeclampsia in control sites), the sample size required for 80% power and 5% significance was 106 in each arm.

Statistical approach

Statistical analyses: Kaplan-Meier curves were derived and Mantel-Cox log-rank test survival analyses performed to describe the primary outcome. Fisher's exact and chi-square tests were used for categorical variables and Mann-Whitney U tests were used for continuous variables.

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To assess the performance of PlGF to identify women who suffered an intrauterine fetal death, an area under the receiver-operator curve (AUC ROC) analysis was performed. Using Prism 5·0 (GraphPad, San Diego, CA), statistical significance was set at p<0·05 for the primary comparison, and p<0·01 for other comparisons (to adjust for multiple comparisons).

Results

During the seven months of the study, the diagnosis of preeclampsia was suspected in 278 and 194 women in intervention and control sites, respectively. These represent 0·87% of 31,993 and 0·57% of 33,841 antenatal visits in intervention and control sites, respectively (Yate's-corrected χ^2 p < 0·0001; relative risk 1·21 (95% confidence interval (CI) 1·13 - 1·31). In addition, this represents a 3·3% detection rate (assuming 8400 women receiving prenatal care in the six intervention sites), compared with a 2·3% (194/8400 women) suspected preeclampsia rate in six control sites (Yate's-corrected χ^2 p = 0·0001; relative risk 1·23 (95% CI 1·09 - 1·37)). Fetal heart sounds were detected using Pinard stethoscopes in all women at eligibility.

Maternal transfer to higher levels of care (primary outcome) was initiated for 133/278 (47·8%) and 20/194 (10·3%) of women in intervention and control sites, respectively (Yates-corrected χ^2 p = 0·0001; relative risk 1·91 (95% CI 1·67 - 2·19)). These represent referral rates of 0·42% and 0·06% of antenatal visits in intervention and control sites, respectively (Yate's-corrected χ^2 p < 0·0001; relative risk 1·79 (95% CI 1·68 - 1·91).

Table 1 describes the baseline characteristics and outcomes of the 278 women with suspected preeclampsia attending for prenatal care at the intervention sites. Compared with 148 women with normal PlGF (≥100pg/ml), the 130 women with low PlGF (<100 pg/ml) were younger, at later gestational age when screened for PlGF, more severely hypertensive, more likely to have a confirmed diagnosis of preeclampsia by either proteinuria or symptoms, especially symptomatic preeclampsia, and more likely to have an increased number of prenatal visits (all p <0·01); they tended to be more often nulliparous (p = 0·0180) and receive antihypertensive medication (p = 0·0191). This detail of clinical data was not available for the women who attended the control sites.

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In terms of the clinic-to-delivery interval, women with low PlGF delivered more quickly (median: 10 days) compared with those with normal PlGF (median: 36 days) (Figure 1(a)). Women with low PlGF delivered at earlier gestational ages (35 vs 37 weeks, respectively (Figure 1(b))), more frequently preterm (85% vs 55%, respectively), and lighter infants (2·5 kg vs 3·1 kg, respectively). Only two (0·7%) women in this cohort received antenatal corticosteroids, although 117 of 278 (42·1%) women delivered before 35^{+0} weeks of pregnancy. Of the 160 (of 242 women who received antihypertensive agents) for whom the antihypertensive agents were recorded, 33 received solely methyldopa, while three received methyldopa and nifedipine, 100 received methyldopa and hydralazine and 21 received methyldopa, nifedipine and hydralazine. Three women received solely hydralazine.

There were three maternal deaths, two were women with normal PlGF (one of whom declined early referral to hospital and arrived moribund; the other declined to remain an inpatient and was lost to local follow-up (moved to South Africa)) and one with low PlGF (in-facility death in the regional tertiary hospital). Twenty-three percent of women with low PlGF suffered an intrauterine fetal death, compared with 6% of women with normal PlGF (p<0·0001). Neonatal survival was similar between groups.

The area under the receiver-operator curve analysis of the performance determined that maternal PlGF predicted both intrauterine fetal death (AUC ROC = 0·78) and perinatal death (AUC ROC = 0·75) (Figure 2). Thirty of 30 of 92 (32·6%) women with PlGF <50pg/ml suffered an intrauterine fetal death, compared with nine of 177 (5·1%) women with PlGF ≥50pg/ml (Yates-corrected χ^2 p<0·0001). Using that cut-off of <50 pg/ml, maternal plasma PlGF has a sensitivity of 76·9% (95% CI 60·7% - 88·9%) and specificity of 74·1% (95% CI 68·0% - 79·5%) in the prediction of intrauterine fetal death.

Discussion

In this implementation study, we have determined that among women with preeclampsia who attended prenatal clinics in Maputo, Mozambique, the introduction of a package of care, including the use of PlGF, was associated with both an increased detection of preeclampsia and an increased number of transfers of care. In addition, low maternal plasma PlGF identified

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women destined to deliver soon and have more complicated pregnancies, as determined previously using masked PlGF results (8). Also, we have determined that maternal plasma PlGF <40 - 50 pg/ml identifies a group of women at exceptionally high risk for suffering an intrauterine fetal death (32·6% of women with PlGF <50 pg/ml).

The incidence of suspected preeclampsia in intervention sites was as anticipated from the literature (12); it is almost certain that the diagnosis was missed in a number of women in control sites. Due to probable incomplete identification of women with suspected preeclampsia in the control sites, direct comparison of the performance of the PlGF assay in terms of reducing the incidence of preeclampsia-related adverse pregnancy outcomes could not be assessed. However, women in the intervention sites were almost twice as likely to be referred to higher levels of care than were women in control sites. The identification of women with pregnancies complicated by preeclampsia and responding to precision risk assessment using PlGF, as achieved in the intervention sites, are critical steps towards reducing direct maternal deaths due to pregnancy hypertension (13).

Incomplete knowledge of the detailed clinical characteristics and outcomes of women who attended for prenatal visits in the control sites is the major limitation of this pragmatic operational pilot study. In addition, the level of confidence in these results might have been improved had a stepped-wedge implementation trial design been used (14).

The exact threshold for raising specific intrauterine fetal death concern requires specific hypothesis-driven research in both general populations and targeted high-risk populations (e.g., preeclampsia, fetal growth restriction, previous intrauterine fetal death) of women. If testing for maternal PlGF can be converted into a whole blood point-of-care assay, we believe that there is great potential for this biomarker of the imperfectly performing placenta to be used at scale to reduce the burden of intrauterine fetal death. Currently, in less-developed settings without access to sophisticated Doppler ultrasound, we believe that a maternal plasma PlGF <50 pg/ml should be considered as a strong indication for initiating delivery.

Although the median number of prenatal care visits was the same in women with normal and low PlGF (median number of visits: 3), there was a significant increase in the number of visits in

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the low PlGF group as a whole (p=0·0006). This is likely to be due to an appropriate response by the woman and her care providers' knowledge about her low PlGF status, although these low PlGF women remained pregnant for about one-third of the time (median: 14 days) than did women with normal PlGF (median: 41 days).

Two hundred and forty-two (87·1%) women with suspected preeclampsia in the intervention cohort received antihypertensive agents, with a trend for more in the low PlGF group (p = 0·0191). This probably reflects higher systolic and diastolic blood pressure readings at the recruitment prenatal visit. However, as any severe hypertension confers as much risk to a pregnancy as the diagnosis of preeclampsia (15), blood pressure should be normalized in all pregnancies complicated by hypertension, using the CHIPS Trial tight control decision algorithm (16). In settings such as these, in which all three delays that contribute to maternal death are operating, tight control (i.e., targeting a diastolic blood pressure of 85 mm Hg, and responding to any systolic blood pressure ≥160 mm Hg) is likely to have benefits beyond those observed in the main CHIPS Trial. Four hundred and sixty-three of the 981 women in CHIPS developed preeclampsia. The preferential use of methyldopa is consistent with knowledge of availability, cost, improved pregnancy outcomes and neurodevelopmental reassurance to seven years of age (16-19).

Although known to be the optimal agent for both the prevention and treatment of eclampsia (20-23), there was very low use of magnesium sulfate in this cohort (4·7% of hypertensive women overall), even though care providers were informed of the PlGF results, and low PlGF is known to identify women at greater risk for adverse events (5;8;9). It is incumbent on those introducing such a new package of care to ensure vertical integration of the health system and that effective messaging around the new technology crosses all levels of the health system to modify caregiving behavior. Unfortunately, we were not able to determine with certainty the incidence of eclampsia within the cohort. Therefore, whether or not low PlGF should be a specific indication for magnesium sulfate use remains uncertain.

The low rate of use of antenatal corticosteroids (0·7%) in this cohort of women is consistent with the findings in our previous Maputo-based study (8) in which only two of 494 women

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(0·4%) who delivered prior to 35^{+0} weeks received corticosteroids (data previously unpublished). Knowledge of low PlGF status did not change the behavior of care providers between the two studies. It should be noted that the Mozambique Ministry of Health has only recently actively implemented the use of antenatal corticosteroids for fetal lung maturation (train-the-trainers workshop, June 5-7, 2017). In addition, the publication of the ACT cluster-randomized trial in 2015 (24) may have impeded corticosteroid use in this setting where most women have somewhat uncertain dates.

Perspectives

There has been increasing evidence for the role of time-of-disease maternal plasma PlGF in identifying incremental maternal and perinatal risks in pregnancies complicated by placental disorders (i.e, preeclampsia, fetal growth restriction and a large proportion of intrauterine fetal death), including in the similar settings in Maputo. To our knowledge, this is the first study to assess the impact of PlGF on clinical practice and outcomes in a less-developed country setting. We have identified that introducing PlGF into clinical care in antenatal clinics is associated with increased identification of women who are deemed to require transfer to higher levels of care. In addition, we have confirmed the ability of low PlGF, measured at time-of-disease, to identify women with pregnancies complicated by preeclampsia who are at increased risk of adverse events. Also, we have identified that a PlGF threshold of 40 – 50 pg/ml identifies a group of hypertensive pregnant women with a one-third risk of losing their fetus to stillbirth. This requires elucidation. This operational pilot provides additional insights to support the createion of a manual of procedures and recommendations for the scale up of the PlGF test to support the time-of-disease assessment of women with suspected preeclampsia, and screening for stillbirth risk, in high-risk pregnancies in Mozambique.

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Disclosures

P. von Dadelszen has been a paid consultant to Alere International. The other authors report no conflicts.

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Highlights

- In urban health centers in Mozambique, introducing PlGF for precision assessment of maternal risks increased referrals of women with preeclampsia to higher levels of care.
- Low PlGF (<100 pg/ml) identifies women at increased risk of adverse maternal and perinatal events
- Stillbirth complicates preeclampsia pregnancies approximately one-third of the time when PlGF <50 pg/ml.
- All women in the study were hypertensive with suspected preeclampsia.
- PlGF values were revealed to the clinical staff as an element of clinical assessment.

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Figure legends

Figure 1. (a) Time from clinic-to-delivery by placental growth factor concentration dichotomized between normal placental growth factor (≥100 pg/ml; median 10 days (blue)) and low placental growth factor (<99 pg/ml; median 36 days (red)). (b) Gestational age at delivery by placental growth factor concentration dichotomized between normal placental growth factor (≥100 pg/ml; median 37 weeks) and low placental growth factor (<99 pg/ml; median 35 weeks).

Figure 2. Area under the receiver operator curve for placental growth factor in predicting intrauterine fetal death (IUFD; purple) and perinatal mortality up to 28 days (PNM; blue). A maternal plasma placental growth factor concentration <41·8 pg/ml has 76·92% (95% confidence interval (CI) 60·67% - 88·87%) sensitivity, 78·2% (95% CI 72·5% - 83·3%) specificity, with a positive likelihood ratio (LR+) of 3·54 for intrauterine fetal death, and PlGF <39·7 pg/ml a 66·7% (95% CI 52·1% - 79·2%) sensitivity, 79·7% (73·9% - 84·8%) specificity and LR+ of 3·29 for perinatal mortality.

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Table 1. Baseline characteristics and outcomes (n (%) or median (interquartile range))

Characteristic	Intervention sites		P-value
	PlGF ≥ 100 pg/mL (n = 148)	PlGF < 100pg/mL (n = 130)	
Baseline characteristics			
Maternal age, yr	29 (24 – 34)	27 (22 – 31)	0·0061
Nulliparous, Y	28 (18·9)	41 (31·5%)	0·0180
Maternal weight, kg	70 (62 – 80) (n=146)	71 (62 – 79) (n=127)	0·6944
Twin pregnancy, Y	2 (1·4%)	7 (5·4%)	0·0875
Gestational age at recruitment, wk	30 (25 – 34)	33 (29 – 35)	0·0002
Blood pressure at recruitment			
systolic blood pressure, mmHg	150 (142 – 162)	157 (146 – 172)	0·0004
diastolic blood pressure, mmHg	94 (90 – 100)	101 (94 – 111)	<0·0001
Preeclampsia, Y	135 (91·2%)	130 (100%)	0·0002
proteinuria ≥1+	32 (21·6%)	67 (51·5%)	<0·0001
preeclampsia symptoms, Y	102 (74·9%)	112 (88·2%)	0·0021
preeclampsia symptoms, n	1 (0 – 2)	2 (1 -3)	<0·0001
New diagnosis of HIV in this pregnancy, Y	39 (21·3%)	30 (19·6%)	0·7865
Serum PlGF, pg/mL	355 (186 – 828)	25·8 (≤12·0 – 58·9)	<0·0001

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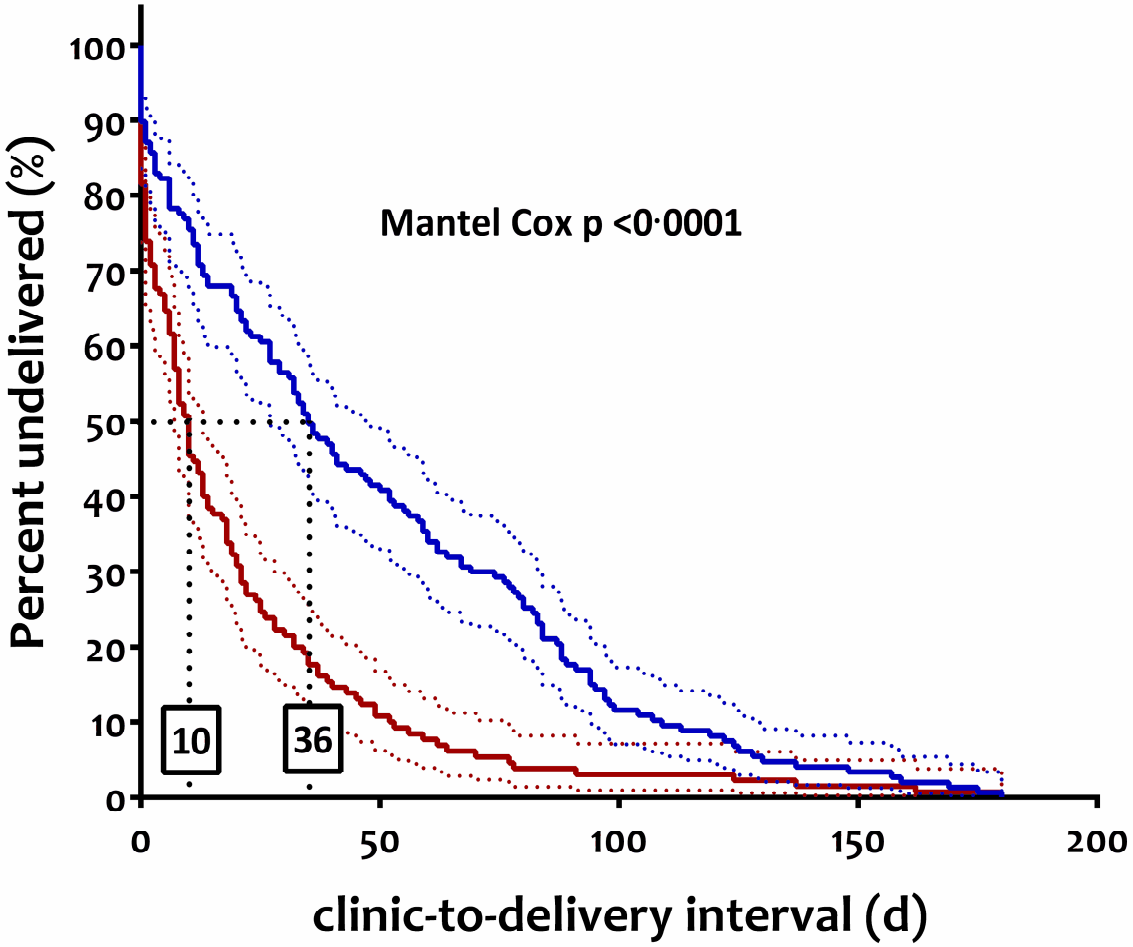
Interventions received			
Number of prenatal visits, n	3 (1 – 4)	3 (2 – 5)	0·0006
Antihypertensive(s), Y	122 (82·4%)	120 (92·3%)	0·0191
Magnesium sulfate, Y	11 (7·4%)	12 (9·2%)	0·6650
Antiretrovirals, Y	72 (48·6%)	77 (59·2%)	0·0917
Dexamethasone, Y	1 (0·7%)	1 (0·8%)	1·0000
Pregnancy outcomes			
Clinic-to-delivery interval, d	36 (11 – 83)	10 (1 – 25)	<0·0001
Gestational age at delivery, wk	37 (34 – 40)	35 (32 – 36)	<0·0001
Preterm birth, Y	81 (54·7%)	110 (84·6%)	<0·0001
Cesarean delivery, Y	41 (27·7%)	43 (33·1%)	0·3608
Birth weight, kg	3·1 (2·7 – 3·4) (n=134)	2·5 (2·0 – 3·0) (n=108)	<0·0001
Maternal mortality, Y	2 (1·4%) (missing = 13)	1 (0·8%) (missing =7)	1·0000
Perinatal and late neonatal mortality, Y	14 (9·6%)	37 (28·5%)	<0·0001
intrauterine fetal death, Y	9 (6·1%)	30 (23·1%)	<0·0001
neonatal death <28d, Y	5 (3·6%) (n=139)	7 (7·0%) (n=100)	0·2475


Percent undelivered (%)
100
90
80
70
60
50
40
30
20
10
0
Mantel Cox p <0·0001
10
36
0
50
100
150
200
clinic-to-delivery interval (d)

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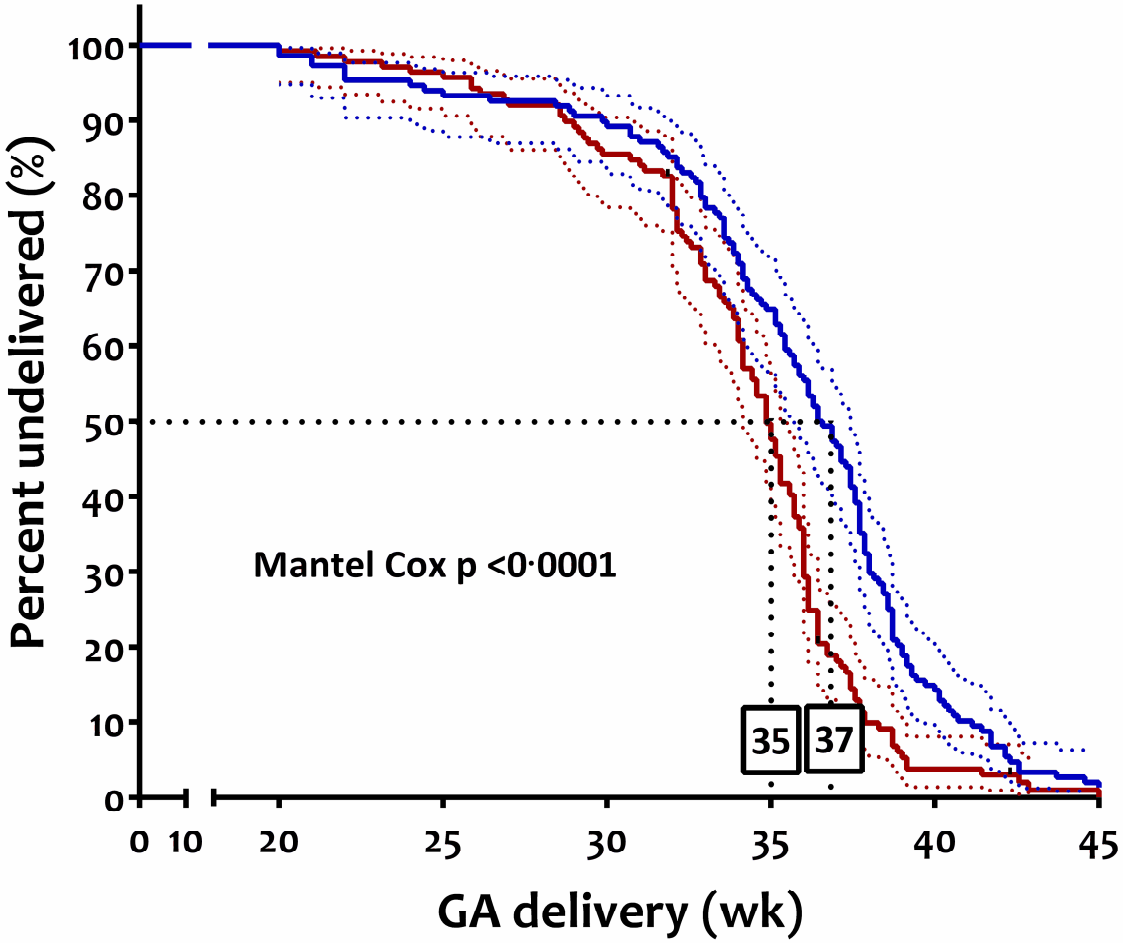

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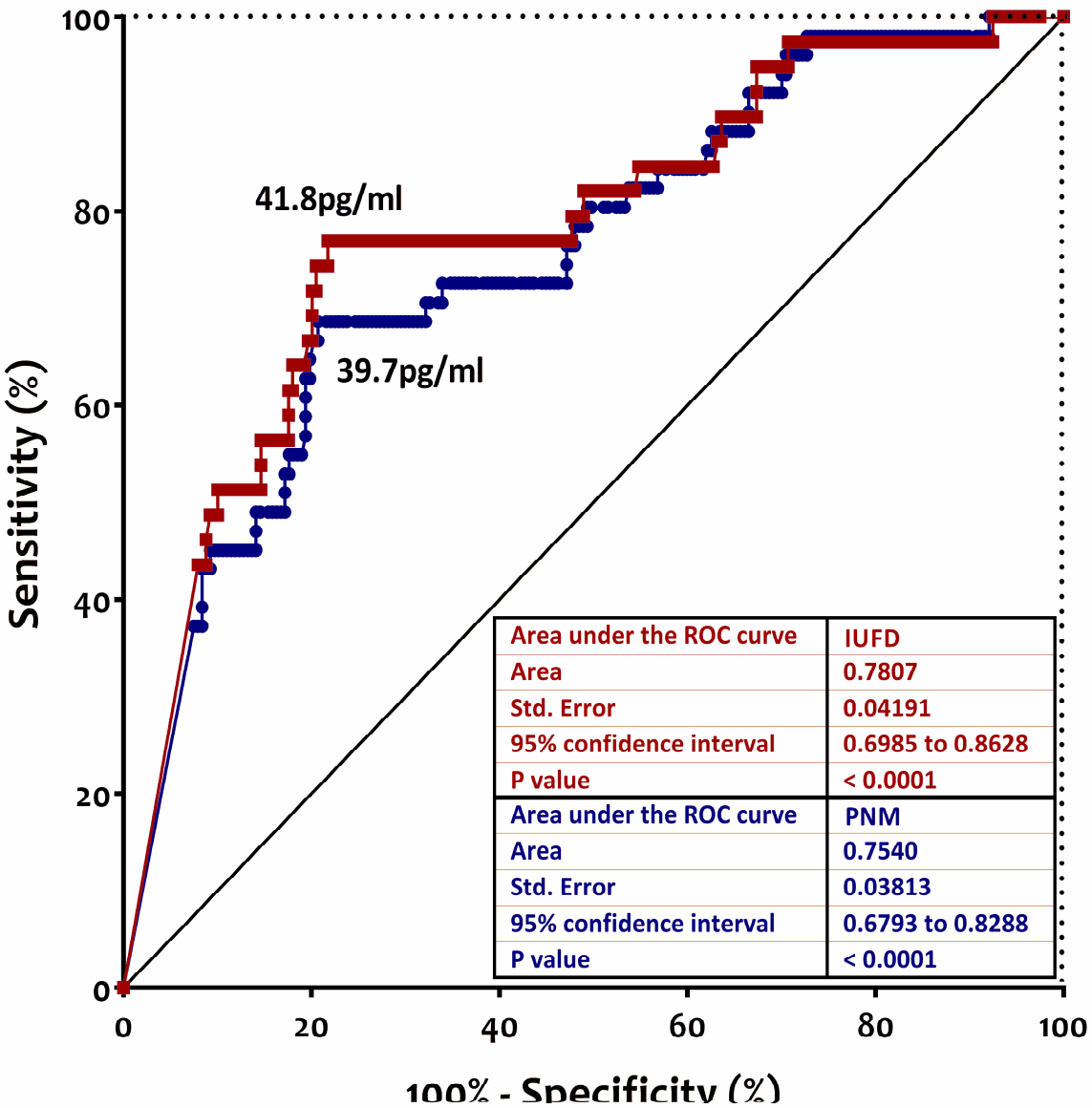

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Highlights

- In urban health centers in Mozambique, introducing PlGF for precision assessment of maternal risks was associated with increased referrals of women with preeclampsia to higher levels of care.
- Low PlGF (<100 pg/ml) identifies women at increased risk of adverse maternal and perinatal events
- Stillbirth complicates preeclampsia pregnancies approximately one-third of the time when PlGF <50 pg/ml.
- All women in the study were hypertensive with suspected preeclampsia.
- PlGF values were revealed to the clinical staff as an element of clinical assessment.

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